Implementation of 21 CFR Part 1271

Martha A. Wells, MPH
Division of Human Tissues
CBER
AATB Annual Meeting
Hollywood, Florida
September 20, 2005

Focus Today

- Regulatory issues and questions
- Exemptions and Alternatives
- Reporting
- Compliance
- Q and A’s

Implementation: 21 CFR Part 1271

- Donor Eligibility (DE) and Current Good Tissue Practices (CGTPs) requirements effective May 25, 2005
- For Human Cells, Tissue and Cellular and Tissue-Based Products (HCT/Ps) recovered on or after this date
- CGTPs “mostly” not effective at this time for reproductive cells and tissues
- 21 CFR Part 1270 requirements still effective for those HCT/Ps procured before 5/25
- Interim Final Rule (IFR) published and effective 5/25
  - Focused on changes for reproductive and hematopoietic stem cell HCT/Ps

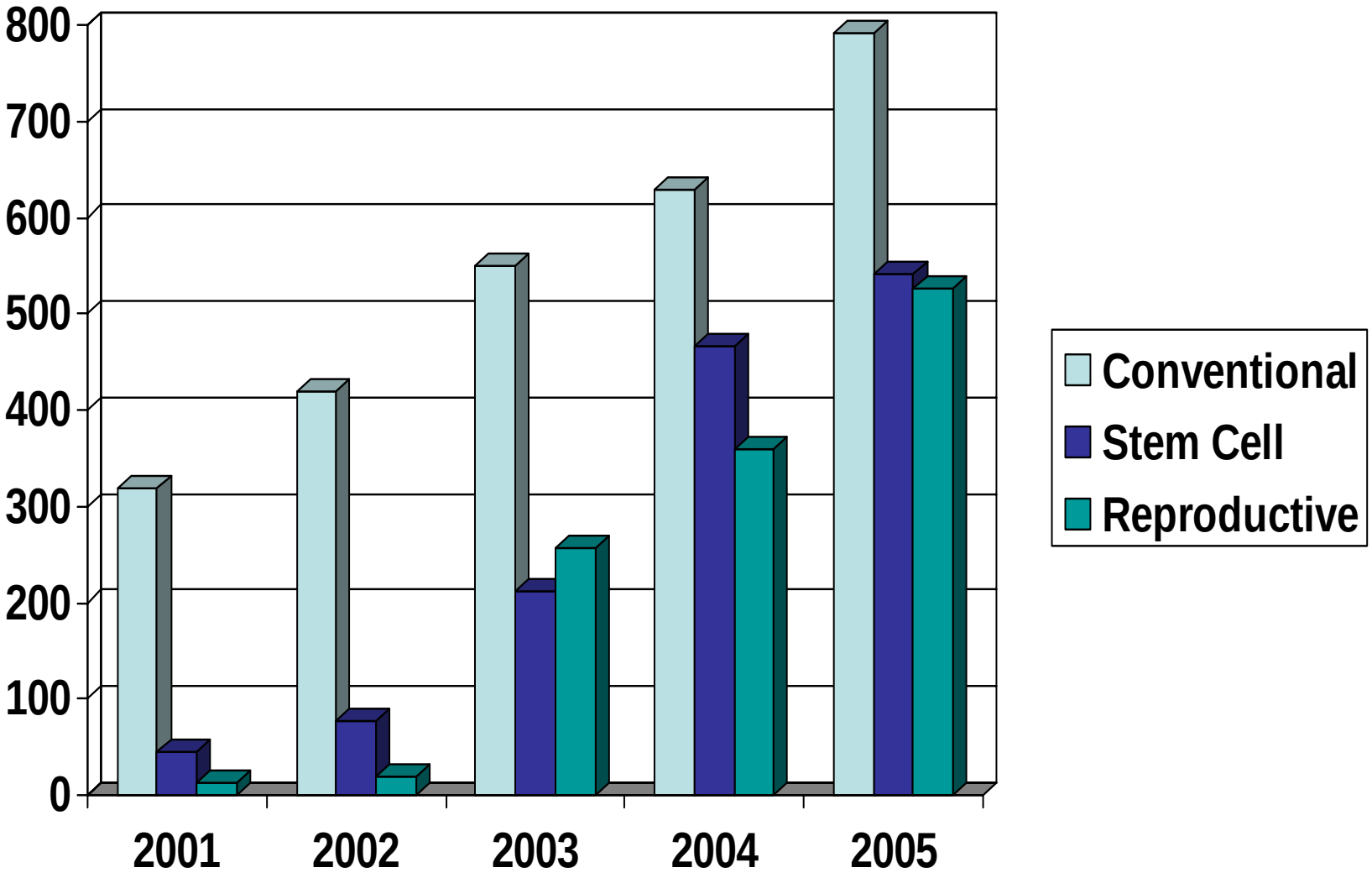
Registration and Listing

- All HCT/P establishments were required to register by March 29, 2004
- Included those
  - Manufacturing medical devices that have an HCT/P component
  - Blood establishments manufacturing hematopoietic stem cells
- Exception if the establishment only manufactures human heart valves and dura mater – until May 25, 2005
  - Next annual update is in December – you should now indicate these HCT/Ps in the "361" column on Form FDA 3356

Registration

- 1970 actively registered establishments
- 188 inactivated – out of business or determined not to be required to register
- Annual registration required in December
- 248 failures to register in December 04
  - Forgot!
  - Form got lost!
  - New reporting official!
  - District office follows up on these
- Listing of registrants and query on the web

Establishments Registering



Registration Questions

- Should donor testing labs and labs performing microbiological testing on HCT/Ps register?
  - YES, donor testing is a manufacturing function and
  - Micro testing is considered processing
- Should an independent sales rep that routinely holds HCT/Ps in his home until delivery to a hospital register?
  - YES- stores and distributes.
  - Should register a legal name of his/her company (not his/her first and last name)
  - Inspected for SOPs, records, environmental monitoring etc

Registration Questions

- Should a hospital with more than 1 type of HCT/P lab (stem cell, reproductive, donor testing) have multiple registrations?
  - NO, only one registration from each physical location
  - Hospital administrator should be involved
- Should a hospital that stores autologous bone flaps register?
  - NO, exemption 1271.15(b) same surgical procedure
  - As long as no additional manufacturing

Registration Questions

- Should a hospital that ships an autologous bone flap to another hospital for implantation in that patient register?
  - NO, if this is a non-routine occurence, the exemption applies, as it is for the same surgical procedure
- Should a hospital that receives qualified HCT/Ps and routinely shares them with other hospitals register?
  - YES, they are now distributors

DE Issues/Questions

- Finalization of the DE guidance – Soon!
- Do establishments need to follow the recommendations if the guidance is not a requirement?
  - Guidance represents FDA's current thinking
  - You may use alternative methods that are as effective to adequately and appropriately reduce the risk of infectious disease transmission – discuss with FDA
- Majority of DE questions concern reproductive HCT/Ps
  - Timing and types of testing and screening
  - Various scenarios using gametes from anonymous, directed and sexually intimate couples
  - Procedures using surrogates/gestational carriers
  - Storage and labeling issues

CGTP Issues/Questions

- Guidance to be drafted
  - Basis will be AATB/EBAA draft Q and A's
  - FDA will review/revise/add/subtract before publication of draft for comment
- What CGTPs do donor test labs and micro test labs have to comply with?
  - Those applicable to their operation
  - Quality program, SOPs, recordkeeping etc.
- Does customized software have to be validated?
  - YES, if you use it to comply with core GTP requirements
  - If off the shelf, then only need to verify that that it performs appropriately - document

CGTP Issues/Questions

- Are vendor qualification and audits required for supplies and reagents?
  - NO, only verification of supplies and reagents
  - Certificates of analysis sufficient
- Do packaging and shipping conditions have to be validated or verified per GTPs?
  - NO, for 361 HCT/Ps process validation only applies to processing
  - Do need to assess if packaging/shipping conditions are designed to protect the HCT/P from contamination and maintains established conditions

CGTP Issues/Questions

- Must quality audits be performed for an outside organization under contract?
  - NO, quality audits (1271.160) are only required for internal operations
  - However, per 1271.150 you must determine that the establishment under contract complies with the applicable GTPs
  - Reliance on AATB accreditation and FDA registration is not sufficient to determine if the establishment is in compliance

Exemptions and Alternatives

- 8 requests received to date
  - 2 not needed because of IFR changes to labeling
  - 1 not needed because the requested tests were already appropriate
  - 5 in progress
- Requests must be accompanied by supporting documentation, including all relevant valid scientific data and must contain either
  - Information justifying the requested exemption or
  - A description of a proposed alternative method

Exemptions and Alternatives

- Requests relevant to DE and GTP requirements
- No time line for FDA response
- If “361” product, biological product or medical device regulated by CBER send to
  - Jesse L. Goodman, M.D., M.P.H.

    Director, Center for Biologics Evaluation and Research

    1401 Rockville Pike, HFM 775

    Rockville, MD 20892
  - Contact me if questions, as DHT maintains files

Exemptions and Alternatives

- If HCT/P is a medical device regulated by CDRH, then request is sent to

  Daniel G. Schultz, M.D.

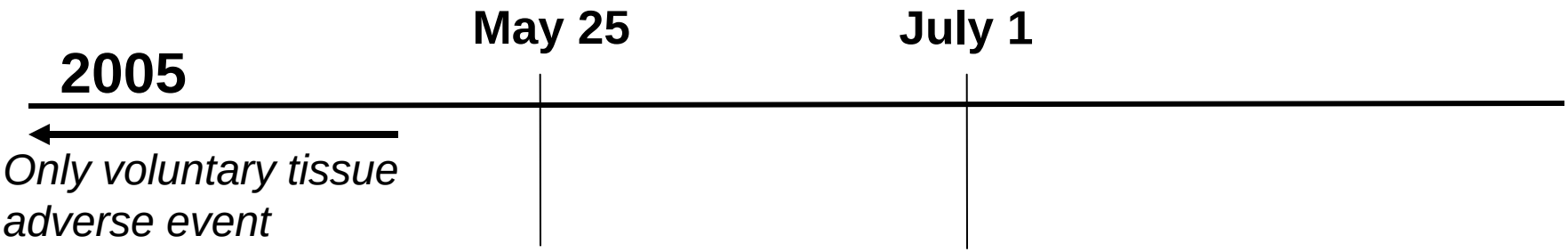
  Director, Center for Devices and Radiological Health

  c/o Director, Program Operations Staff

  9200 Corporate Boulevard, HFZ-402

  Rockville, MD 20850
- Specify the part of 1271 you are requesting the exemption or alternative for
- Include your FEI number from your registration form
- If the establishment is not registered (only investigational products), include the relevant regulatory submission number (e.g., IND, IDE, BLA, PMA or 510(k))

2005 New Reporting Requirements



FDA's Current Good Tissue Practices (21 CFR 1271)

Reporting Requirement:

HCT/P manufacturers are required to report to FDA certain adverse reactions involving a communicable disease.

JCAHO Tissue Issuance and Storage Standards (PC.17.30)

For organizations that store or issue tissue (*e.g.*,hospitals):

- Procedures must be in place to investigate recipient adverse events
- Cases of post-transplant infections or adverse events are promptly reported to the source facility

FDA's Current Good Tissue Practice Reporting Requirement: 21 CFR 1271.350 (a)

- Manufacturers must ***investigate:***
  - ***Any*** adverse reaction involving a communicable disease related to an HCT/P that they made available for distribution.
- Manufacturers must ***report*** to FDA
  - An adverse reaction involving a communicable disease if it
  - Is life-threatening
  - Results in permanent impairment of function or perm damage to body structure;
  - Necessitates medical or surgical intervention, including hospitalization

HCT/P Adverse Reactions

- Adverse reaction means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response
- To report adverse reactions to FDA, manufacturers must submit a MedWatch 3500A to FDA within **15** days of receipt of information

Reporting an Adverse Reaction to FDA?

- Medwatch Forms being revised – October?
- For Voluntary Reporters
  - Health care providers and consumers
  - Use Form FDA 3500 (MedWatch)
  - Also promptly report to HCT/P establishments
  - End users are encouraged to forward reports to the manufacturer as complaints
  - Can also report directly to FDA
- For HCT/P manufacturers
  - Use Form FDA 3500A (MedWatch)
  - Send 2 copies of each report to

    Center for Biologics Evaluation and Research (CBER)

    1401 Rockville Pike, HFM-210

    Rockville, MD 20852

Reporting

- 1271.350(a) only for “361” tissues
- Other HCT/Ps must follow other regulations for reporting, but MedWatch form can be used
  - Adverse event (reaction) does not have to be communicable disease specific
- If HCT/P regulated as a biological product
  - 21 CFR 312.32, 312.64, 314.80 or 600.80
- If HCT/P regulated as medical device
  - 21 CFR 803 or 812

MedWatch forms: http://www.fda.gov/medwatch/

U.S. Food and Drug Administration

Department of Health and Human Services

FDA Home Page | About MedWatch | Contact MedWatch | MedWatch Partners

MEDWATCH The FDA Safety Information and Adverse Event Reporting Program

Search MedWatch Go

MedWatch Home | Safety Information | Submit Report | How To Report | Download Forms | Join the E-list

Join the E-list
Get safety alerts by e-mail

Welcome to MedWatch, your Internet gateway for timely safety information on the drugs and other medical products regulated by the U.S. Food and Drug Administration.

What's New

Cordarone (amiodarone HCl) - New Medication Guide issued, to be provided with each prescription dispensed to patients.
(Posted 01/10/2005)

Avastin (bevacizumab) - WARNINGS, PRECAUTIONS, ADVERSE EVENTS, and DOSAGE AND ADMINISTRATION sections of labeling updated to describe arterial thromboembolic events when Avastin is used in combination with intravenous 5-fluorouracil–based chemotherapy.
(Posted 01/06/2005)

American Health & Herbs Ministry Eye Rinse Products - Voluntary recall

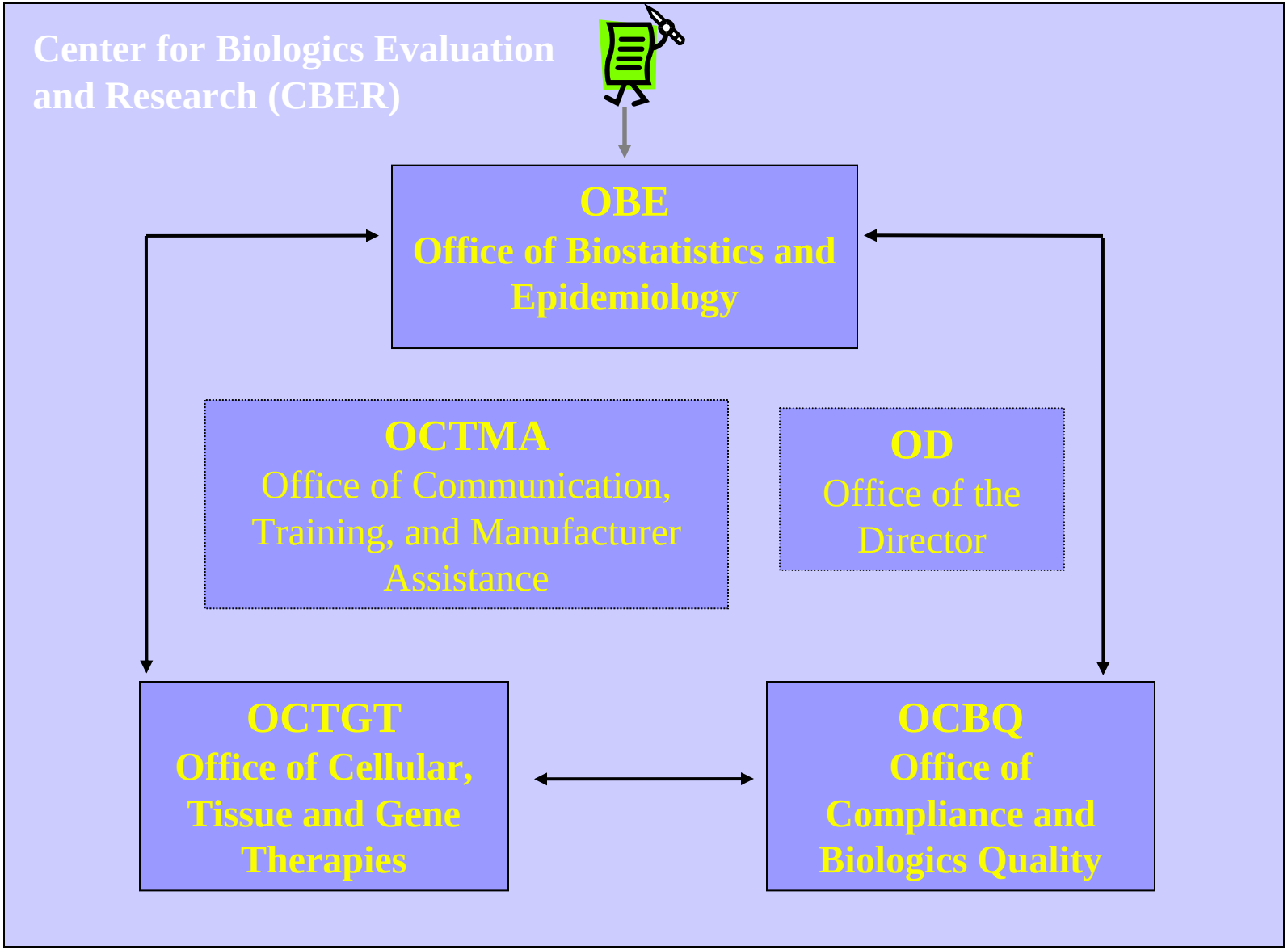
Safety Information

Medical Product Reporting

CBER's Tissue Safety Team

- Formed to monitor adverse reaction reports and to coordinate any related activities
- Coordination within CBER but contacts with other Centers and agencies such as CDC, HRSA
- Issued a Standard Operating Procedures and Policies (SOPP) 8508 for handling adverse reaction reports related to "361" HCT/Ps (http://www.fda.gov/cber/regsopp/8508.htm).
  - Includes appendices with points of contact
- Email address for questions on adverse reaction reporting is TST@cber.fda.gov

FDA's Tissue Safety Team



HCT/P MedWatch Reports to CBER

- Since May 25, 2005:
  - 46 MedWatch Reports
    - Tissues: 17
    - Cells: 17
    - Devices: 6
    - Devices/Tissues: 6

Tissue MedWatch Reports to CBER

17 Tissue Reports

- 6 from manufacturers
- 11 from voluntary reporters

- 7 with Tissue Safety Team follow-up

Tissue MedWatch Reports to CBER

17 Tissue Reports

- Post-transplant infections 5
- Positive pre-implant culture, no event 4
- Non-infectious adverse events 5
- Discordant serology 1
- Product problems 2

  (mis-labeled, irregular)

Tissue MedWatch Reports to CBER

- 5 post-transplant infections

  Tibialis tendon, cornea, saphenous vein, femoral vein, skin graft

  – 2 required explantation

  – 3 required incision and drainage, debridement

    - 2 went to OR and underwent anesthesia for procedure

  – 3 reported by manufacturers, but

  – 0 were required under 21 CFR 1271 because tissue recovery date before 5/25/05

HCT/P Deviations: 1271.350(b)

- Defined as an event that represents a deviation from applicable regulations or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or
- As an unexpected or unforeseeable event that may be related to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination
- Can be detected before use or in the operating room

HCT/P Deviations

- Manufacturer must investigate deviations related to a **distributed** HCT/P
- Manufacturer must report to FDA any deviation that occurred in their facility or in one under contract to them within 45 days of the discovery of the event – must be core GTP related
- On line reporting: http://www.fda.gov/cber/biodev/biodev.htm
  - HCT/P codes
  - HCT/P deviation codes related to core GTPs
  - Form FDA 3456
- Email address for questions

  HCTP_Deviations@cber.fda.gov

HCT/P Deviation Reporting

- Encourage end users to forward reports on possible deviations to the manufacturer as complaints
- Guidance will be developed
- Reports will be trended
- 34 reports received to date (some multiple products)
- Products involved
  - 20 hematopoietic stem cells
  - 10 cornea
  - 9 musculo-skeletal

HCT/P Deviation Reports

- Reports to date included
  - Autopsy report not reviewed prior to distribution of product- autopsy revealed possible IV drug use
  - Conflicting medical history not resolved prior to distribution of product - sex in exchange for drugs
  - Incorrect product designated for quarantine due to pending completion of donor eligibility determination
  - Viral marker positive – not known at the time of eligibility determination

HCT/P Deviation Reports Not Reportable

- No products were distributed
- Not associated with disease transmission or contamination
- Not related to core GTP
- Problem corrected prior to distribution of product
- Positive pre-implant culture is in general not reportable as a deviation
  - Unless a complaint results in an investigation that reveals a departure from GTPs or
  - If the recipient had an adverse event, then report as an adverse reaction not HCT/P deviation

Inspections and Compliance Activities

- Compliance Program Guide 7341.002 published July 1, 2005
  - Instructions to District field investigators on how to conduct HCT/P inspections
  - For “361” tissue recovered after May 25, 2005
- Guide 7341.002A published May 4, 2003 for HCT/Ps recovered before May 25, 2005
- Training for district investigators
  - Recent updates for those previously trained
  - Included professionals from reproductive tissue and hematopoietic stem cell establishments

Top Inspectional Observations 2005 (Applicable to Establishments Regulated under 21 CFR Part 1270 as of 8/16/05)

- (35) Failure to prepare, validate, or follow written procedures for prevention of infectious disease contamination, cross-contamination during processing
- (22) Failure to prepare, or follow written procedures for all significant steps for obtaining, reviewing, assessing the relevant medical records of a donor
- (18) Failure to maintain records which are accurate, indelible, legible

More Observations

- (15) Records fail to identify the person performing the work, the date the work was performed and the particular tissue involved
- (14) Records fail to include documentation of destruction or other disposition of human tissue.
- (11) Failure to prepare and/or follow written procedures for designating and identifying quarantined tissue
- (9) Tissue intended for transplantation was not accompanied by a summary or copies of the donor’s relevant medical records

More Observations

- (8) Failure to test donor specimens for communicable viruses using licensed donor screening tests in accordance with manufacturers' instructions
- (7) Failure to prepare and/or follow written procedures which conform to all significant steps specified in the package inserts for infectious disease testing
- (7)Failure to maintain records concurrently with the performance of each significant step in the performance of infectious disease screening or testing of donors

Inspection of Tissue Establishments

Year	# Inspections	FDA-483's Issued
1994-97	111	55 (49.5%)
1998	111	50 (45%)
1999	65	31 (47.7%)
2000	93	36 (38.7%)
2001	132	51 (38.6%)
2002	165	48 (29%)
2003	227	58 (25.5%)
2004	188	48 (25.5%)
2005 (to 8/15)	191	33 (17.3%)

Inspections Since May 25, 2005

- 39 inspections completed (by 8/17)
- 18 completed inspection reports forwarded
- 2 received 483s
- 46% involved only tissues recovered before 5/25
- Discussion items – not cited
  - Need to have complaint files and procedures
  - Recordkeeping practices for receipt, distribution and tracking were not adequate
  - Accompanying records need to have statement that viral marker testing was done in a CLIA certified lab

Enforcement Actions: FY 2005

- Before 5/25/05
  - 0 Class I Recalls (reasonable probability that use or exposure will cause serious adverse health consequences or death)
  - 21 Class II Recalls (use or exposure may cause temporary or medical reversible adverse health consequences or probability of serious adverse health consequences remote)
  - 1 Class III Recall (use or exposure not likely to cause…)

Enforcement Actions: FY 2005

- After 5/25/05 – 3 Class II Recalls
  - 2 were for products recovered prior to 5/25
  - 1 for product recovered after 5/25
    - Autopsy results were not obtained prior to tissue release as per SOP
    - Autopsy was performed and indicated donor was likely IV drug user

For Further Information

- http://www.fda.gov/cber/tiss.htm
  - May be adding pages for
    - Adverse reaction reporting
    - Exemption and alternative requests
    - Comprehensive listing of recommended testing
      - For syphilis, chlamydia, gonorrhea and CMV
      - Currently can find HIV, HTLV and Hepatitis at http://www.fda.gov/cber/products/testkits.htm
      - Currently can find tests approved for cadaveric and other living donors at http://www.fda.gov/cber/tissue/prod.htm
- wells@cber.fda.gov, 301-827-6106